REMARKS

This response is filed in reply to the Office Action mailed May 1, 2003. Claims 22-29 and 36 have been canceled. Claims 1-9, 15, 16, 30, 31, 37, 38, 39, 43 and 45 have been amended. Claim 63 has been added. Support for the amended claims and new claim can be found throughout the specification. Specifically, support for a heterologous nucleic acid sequence that "comprises a structural gene that encodes a biologically active protein..." as set forth in claim 1 can be found at page 21, lines 5-22.

This response is accompanied by a declaration from Dr. Amy Lee under 37 C.F.R. §1.132. In addition, this response is accompanied by Exhibits A (Ting and Lee, *DNA*, **7**:275-286), B (Resendez et al., *Mol. Cell Biol.*, **8**:4579-4584), and C (Li et al., *Mol. Biol.*, **14**:5533-5546).

No new matter has been added. Claims 1-9, 15, 16, 30-35, 37-43, 45, 46 and 63 are pending and at issue. Applicant requests reconsideration of the present application.

Priority

The Office Action alleges that the provisional application upon which priority is claimed "fails to provide adequate support under 35 U.S.C. §112 for claims of this application."

Applicants respectfully disagree. The provisional application (60/141,505) disclosed novel compositions and methods for anti-cell proliferation therapy. The compositions comprise stress-responsive non-coding regulatory sequences that provide enhanced gene expression in a variety of tumors. The expression of a heterologous polypeptide that activates a therapeutic agent within a tumor environment was shown to inhibit the ability of the tumor to continue to grow.

Applicants priority document provided exemplary compositions and methodology for expressing a heterologous polypeptide from a stress-responsive non-coding regulatory sequence in an environment of fast-growing cells. Applicants submit that the written disclosure of the priority document is supplemented by the knowledge held by one of ordinary skill in the art. The skilled artisan is one who is knowledgeable about basic laboratory/research protocols. It is well settled law that an Applicant need not include disclosure that was well known in the art. It was well within the capabilities of the skilled artisan, at the time the priority document was filed, to take such teachings and modify the protocol, for example, the heterologous polypeptide, therapeutic agent, and/or delivery conditions, to obtain the methods of the invention. Thus, the the provisional application provided sufficient guidance for one of ordinary skill in the art to practice the claimed invention.

Accordingly, Applicant's maintain that the provisional application filed June 28, 1999, fully supports the breadth of the originally filed claims as well subsequently amended claims.

Claim Objections

Claims 26-37 are objected to because they depend from non-elected claim 17. Claims 26-29 have been canceled. The remaining claims have been amended to delete any reference to claim 17. Claim 8 is objected to for using the term "or" following the phrase "a group consisting of." Claim 8 has been amended to delete "or" and recite "and."

I. Rejections under 35 U.S.C. §112, First Paragraph

Written Description

Claims 1-9, 15, 16, 22-24, 26-43 and 45-46 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is moot with regard to canceled claims 22-24, 26-29 and 36. Applicant traverses this rejection as applied to the amended claims.

The present specification provides the first evidence that a vector containing a structural gene operably linked to a grp78 stress-responsive non-coding sequence can be used to express a biologically active protein capable of converting a non-therapeutically active compound to a therapeutically active compound in vivo. Once expressed under conditions that activate the stress responsive non-coding sequence, the biologically active protein converts a pro-drug to a compound capable of preventing cell growth in a tumor environment. The skilled artisan would recognize that the Applicant was in possession of the claimed vector given the information disclosed in the specification. Nevertheless, in order to expedite prosecution, the claims have been amended to recite a "grp78 stress-responsive non-coding sequence" comprising at least two endoplasmic reticulum stress elements. In view of the amendments to the claims, Applicant requests that this rejection under §112 be withdrawn.

Claims 2, 3, 22-24, 26-43 and 45-46 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is moot

with regard to canceled claims 22-24, 26-29 and 36. Applicant traverses this rejection as it may apply to the amended claims.

Specifically, the Office Action alleges that the specification does not provide sufficient description of a genus of grp78 promoter sequences. Applicant disagrees and notes that the standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, (Fed. Cir. 1989); MPEP §2163.02. The "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 para. 1 'Written Description Requirement' (66 Fed. Reg. 1099)" clearly indicate that a written description "review" must be conducted from the standpoint of one of skill in the art at the time the application was filed. The Examiner is required to consider both (i) the field of the invention and (ii) the level of skill and knowledge in the art, keeping in mind the premise that there is an inverse correlation between the level of skill and knowledge in the art and the specificity of the disclosure necessary to satisfy the written description requirement.

A person skilled in the art of gene expression would clearly recognize that the presently claimed vectors and constructs encompassed the use of a genus of grp78 promoter sequences, not just those specifically disclosed in the present specification. For example, the present disclosure describes a vector comprising a rat grp78 promoter fragment spanning nucleotides -520 to +175 of the grp78 gene (page 7, lines 12-15; page 68,lines 3-10). The disclosure further describes a transgene construct comprising about 3000 base pairs of a rat grp78 regulatory sequence (page 10, lines 4-10 and Figure 7). However, the skilled artisan would recognize that the nucleic acid vectors and constructs of the invention are not limited

solely to rat grp78 promoter, or specifically described sequences thereof, because the grp78 gene has been identified and sequenced from a number of different mammalian species. Further, the promoter sequences of the various grp78 genes share significant amounts of structural and sequence homology.

The publications which accompany the present response as Exhibits 1-3 provide support for the proposition that the Applicant is entitled to the use of a genus of grp78 promoters in the claimed vectors and constructs. Exhibit A (pages 280-281) shows the sequence of the human grp78 gene and promoter sequence (page 284, Figure 7A) and further shows a comparison of the human and rat grp78 promoter sequences. Exhibit B (page 4582, Fig. 5) shows the structural and sequence similarities between human and rat grp78 promoter sequences. Exhibit C (page 5538, Fig. 3) demonstrates that the human grp78 promoter sequence contains consensus sequences needed to facilitate transcription. All of the previously discussed publications were available to the skilled artisan as of the filing date of the present application.

Applicant is not claiming a grp78 promoter sequence, but rather vector or construct containing such a promoter. Applicant is not required to recite every possible grp78 promoter sequence derived from all possible species from which the promoter has been isolated. On the contrary, in view of the knowledge in the art and skill of the practitioner considered in the totality of the circumstances, Applicant has adequately described the grp78 promoter for the purposes of section 112, first paragraph.

In view of the amendments to the claims, and in light of the above discussion, Applicant requests that this rejection under §112 be withdrawn.

Enablement

Claims 1-9, 15-16, 22-24, 26-43 and 45-56 stand rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to enable one to make and use the invention commensurate in scope with the claims. This rejection is moot with regard to canceled claims 22-24, 26-29 and 36. Applicants traverse this rejection as it may apply to the amended claims.

Specifically, the Office Action alleges that since the claimed invention is not supported by a sufficient written description (for possession of a genus of stress-responsive non-coding regulatory sequence and/or a genus of grp78 promoters) one skilled in the art would not have known how to make and use the claimed invention. Applicant submits that the test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. The amount of experimentation that is permissible to provide enablement depends upon: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims.

The claimed vectors and constructs should not be limited only to those sequences disclosed in the specification (i.e., the rat grp78 promoter sequence) because it would not require undue experimentation to identify additional grp78 promoter sequences that would function in the claimed vectors and constructs. In fact, it would not require any experimentation at all. As noted above (see *Written Description* discussion), the nucleic acid sequence and structural components of the grp78 gene and associated promoter are known to the skilled artisan.

Moreover, the specification of the present application clearly indicates that the grp78 promoter is responsive (i.e., will activate transcription) in a cellular environment that is "stressed." Thus, the skilled artisan can easily identify those grp78 promoter sequences that will function in a vector or construct of the invention by simply combining the information provided in the disclosure with the knowledge already in possession of the artisan.

With respect to claims 36-43 and 45-46, the Office Action alleges that specification does not provide guidelines on the type of vector, the route and course of delivering the vector, trafficking of genetic material, or expression levels of the DNA sequence encoding a therapeutic protein to be delivered to a mammal that correlates with a useful treatment effect. In addition, the Office Action alleges that the claimed methods are not enabled for the treatment of any cell proliferative disorder in a subject.

With regard to the treatment of any cell proliferative disoprder, Applicant notes that claims 37 and 38 have been amended to recite a method of using a therapeutically effective compound that "inhibits cell proliferation associated with glucose starvation" in a subject. Applicant submits that the claimed methods are clearly enabled for the treatment of a cell proliferative disorder associated with glucose starvation because the grp78 promoter sequence is activated under such conditions.

With regard to the type of vector, the route and course of delivering the vector, trafficking of genetic material, or expression levels of the DNA sequence encoding a therapeutic protein to be delivered to a mammal that correlates with a useful treatment effect, Applicant notes that the in vitro and

in vivo studies provided in the specification confirm that the grp78 promoter is capable of inducing a high level of HSVTK expression within the tumor environment, leading to complete eradication of sizable tumors in their syngeneic host after GCV treatment (see page 81, lines 5-15 and Figure 5).

An in vitro bystander effect resulting from the expression of HSVTK in cells transduced with a vector of the invention is clearly demonstrated in Figure 3, Panel C. In vivo, the tumoricidal activity of the HSVTK/ganciclovir system is attributable, in part, to the bystander effect. In dividing cells, the phosphorylated ganciclovir inhibits DNA synthesis. This effect is not confined to cells that are directly transduced with HSV-TK, as neighboring cells are also affected. Transfer of the phosphorylated ganciclovir between cells ("metabolic cooperation") via gap junctions has been proposed as a possible mechanism. Phagocytosis by neighboring cells of ganciclovir phosphate-containing apoptotic vesicles (from dying transduced cells) also has been proposed. The bystander effects of a suicide gene, such as HSVTK, clearly shows that a vector of the invention can provide a therapeutic effect to those cells that are not directly transduced by a vector of the invention, but are in proximity to such a cell. One of ordinary skill in the art would expect that the successful in vitro and in vivo experiments described in the present application would show that the vectors would have a therapeutic effect when administered to a human patient, i.e., that there would be a reasonable correlation between the in vitro and in vivo data and clinical human effectiveness.

The Office Action states that methods of treatment involving gene therapy suffer from major deficiencies including poor gene expression and poor delivery. The Office Action appears to suggest that, absent actual clinical data supporting

the efficacy of a claimed gene therapy-related treatment, the method is not enabled because gene therapy is unpredictable. However, the law is clear that when those having skill in this art are fully able to utilize claimed subject matter as described in the specification, clinical testing should not be made a prerequisite to patentability. See In re Hartop, 311 F.2d 249, (CCPA 1962) and Ex parte Rubin, 5 USPQ 2d 1461 (BPAI, 1987). Applicant has provided cell culture and animal studies which support the conclusion that the claimed methods of treatment are applicable to human subjects for the treatment of cell proliferative disorders. Current case law recognizes that there may be sufficient correlation between animal models and other animals and humans. The issue of "correlation" is related to the issue of the presence or absence of working examples, which are clearly provided in the present specification. The "Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, first paragraph -- Enablement Chemical/Biotechnical Applications" specifically indicate that an in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" because that example "correlates" with a disclosed or claimed method invention.

Applicant submits that the law regarding enablement under §112 is clear. First, it is not necessary to describe and prove actual results of every possible manipulation, combination or variation of vectors of interest and animal species in order to establish enablement of an invention. Nor must there be any indication in the specification that the composition of the invention has actually been reduced to practice for all of the envisioned applications (for example, all grp78 non-coding regulatory sequences of interest). Section 112, first paragraph, requires that the specification contain a description

of the invention, and of the manner and process of making and using it, sufficient to enable a person skilled in the art to make and use the invention. The specification thoroughly describes a vector that can be used to transduce a cell for the purpose of obtaining a therapeutic effect. The amended claims reflect the scope of the specification. Accordingly, Applicant requests that the rejection under §112 be withdrawn.

II. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 2, 3, 23, 36-43 and 45-46 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is moot with regard to canceled claims 23 and 36. Applicants traverse this rejection as it may apply to the amended claims.

The Office Action indicates that the recitation of "the glucose responsive protein 78 promoter" in claim 2 does not have sufficient antecedent basis in claim 1 or claim 2. Claims 1 and 2 have been amended to delete the noted phrase.

Claims 37 and 38 allegedly fail to recite necessary steps. Claims 37 and 38 have been amended to recite steps that relate back to the preamble. Support for the recitation of

> "...activating the glucose responsive protein 78 (grp78) non-coding regulatory sequence such that the heterologous nucleic acid sequence comprising a structural gene that encodes a biologically active protein is expressed..."

can be found at page 32, lines 16-21 of the specification.

Support for the recitation of

> "...contacting the cell with a non-therapeutically effective compound that is subsequently converted

> to a therapeutically-effective compound by the biologically active protein..."

can be found at page 21, lines 10-22 of the specification.

Accordingly, Applicant requests that the rejection under §112, second paragraph, be withdrawn.

III. Rejection Under 35 U.S.C. §§102 and 103

Claims 1, 2, 4-9, 15-16, 22-24, 26-29, 31, 35-40, 42-43 and 45 stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by or, in the alternative, under 35 U.S.C. §103(a) as allegedly obvious over Gazit et al. (*Cancer Research*, **59**:3100 (July 1, 1999)). This rejection is moot with regard to canceled claims 22-24, 26-29 and 36. Applicants respectfully traverse this rejection.

Applicant's note that a declaration by Amy Lee, M.D., under 37 C.F.R. §1.132 accompanies the present amendment. In view of the declaration, Applicant requests that these rejections be withdrawn.

In summary, for the reasons set forth herein, Applicant maintains that claims 1-9, 15, 16, 30-35, 37-43, 45, 46 and 63 clearly and patentably define the invention. Applicant requests that the Examiner reconsider the various grounds set forth in the Office Action and allow the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative can be reached at (858) 678-5070. Enclosed is a $210.00 check for the Petition for Extension of Time fee. Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 10/1/03

Michael Reed, Ph.D.
Reg. No. 45,647

Fish & Richardson P.C.
Customer Number: 20985
4350 La Jolla Village Drive, Suite 500
San Diego, CA 92122
Telephone: (858) 678-5070
Facsimile: (858) 678-5099
10296093.doc